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# The risk of thromboembolic events in kidney transplant patients

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**Little is known about the risk of venous thrombosis following kidney transplant. To determine this we estimated the risk of thromboembolic events (TEs) in a cohort of consecutive patients who underwent kidney transplantation at a single tertiary care center over an 11-year period and calculated standardized incidence ratios (SIRs) for a first TE in kidney transplant recipients compared with the general population. We then performed a nested case–control study and compared patients with and without TEs to identify risk factors for thrombosis. Among 913 kidney transplant recipients (KTRs), 68 patients developed these events. The SIR for TEs in KTRs compared with the general population was 7.9 over the duration of follow-up. The risk was particularly higher in the first post-transplant year (SIR 26.1) but remained elevated afterward (SIR 5.2). Hospitalization, use of sirolimus, low hemoglobin level, and use of renin–angiotensin system inhibitors were independently associated with these events. When cases of TEs that occurred during hospitalization were excluded, the risk of these events remained elevated. The risk of TEs in KTRs was eightfold higher than in the general population but not fully explained by the increased risk associated with hospitalization. Our results underscore the important risk of thrombosis in patients who received a kidney transplant, making vigilance mandatory especially during hospitalization.**

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Deep venous thrombosis (DVT) and pulmonary embolism (PE) are two phenotypes of the same thromboembolic disease. If untreated, this disease has a high mortality.[1] Earlier studies have documented an increased risk of thromboembolic events (TEs) after kidney transplantation (KT).[2,3] Although in the first months after transplantation the risk of TE can be related to the transplant surgery, there seems to be an increased long-term TE risk in kidney transplant recipients (KTRs).[4] The magnitude and the determinants of the increased TE risk after KT are poorly defined. Moreover, in the general population, a major risk factor for TE is hospitalization.[5] It remains unknown whether the relatively high frequency of hospitalization in KTRs may explain the persistently elevated TE incidence in this patient population.

Although traditional risk factors for TE such as age, history of TE, and malignancy[2,3] have been linked to TE in KTRs, little is known about the effect of transplant-specific factors on TE risk. Although various immunosuppressive agents have been shown to possess procoagulant effects,[6] their effect on TE risk in KTR is unknown. For example, although sirolimus, which is increasingly being used for maintenance immunosuppression in KTRs, has been linked to an increased TE risk in cardiac and lung transplant recipients, an association with TE in KTRs has never been shown.[7,8] A recent study reported that TE was more common in KTRs with low estimated glomerular filtration rate (eGFR $<30$ ml/min per 1.73 $m^2$) 1 year after transplantation compared with patients with better graft function.[9] In another report, the use of a vitamin D receptor activator in combination with dual renin–angiotensin system (RAS) inhibitor seemed to be protective for TE.[10] As most studies measured putative risk factors at the time of transplantation instead of measuring them at or close to the time of TE, a pathophysiologically relevant exposure time window is lacking from previous reports.[2,9]

Hence, we undertook the present study to determine the magnitude and the secular trends of the increased TE risk observed after renal transplantation as compared with the risk of TE in the general population. We also aimed to determine whether the increased risk was explained by an

increased probability of hospitalization in KTRs, and we identified risk factors for TE in this patient population.

## RESULTS

The cohort consisted of 913 patients who had 979 renal transplantations. The median follow-up was 5.9 years (range 0–22), with a total of 6760 person–years (p–y). The mean age at transplantation was 47 ( ± 12) years, and 63% of patients were men. In all, 68 patients developed a TE (1.0/100 per year), among whom 42 were diagnosed with DVT alone, 21 with PE alone, and 5 with both DVT and PE. The thrombus was located in the proximal veins in 85% of the subjects with DVT. Nine patients had recurrent TE events. Among the first TE events, 84% were initially treated with unfractionated heparin followed by warfarin, and 9% were treated with unfractionated heparin alone. The mean duration of therapy was 5 months for DVT and 6 months for PE for patients treated with warfarin. The six patients undergoing heparin treatment had a treatment duration varying from 1 month to life long. Loss to follow-up occurred in 26 patients (2.8% of the cohort). Although only one subject died of his TE, patients who experienced a TE had an increased mortality risk (hazard ratio 2.1 (1.2–3.8)).

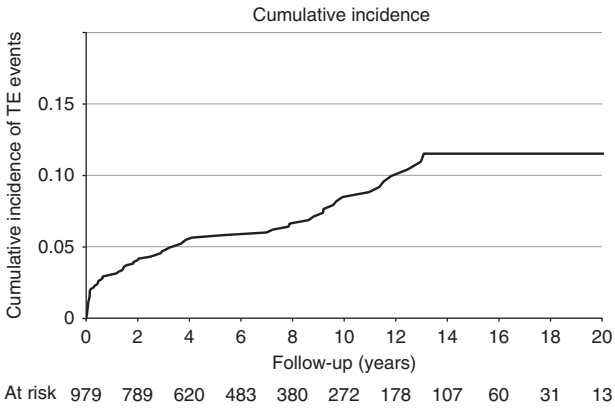


**Figure 1 | Graph illustrating the cumulative incidence of TE events (left *y* axis) per year after renal transplantation (right *y* axis).**

### The risk of TE is elevated in the first year after KT but remains higher than that in the general population throughout follow-up

The cumulative incidence for TE at 1, 5, and 10 years after renal transplantation was 3.0, 5.8, and 8.4% (Figure 1). The standardized incidence ratio (SIR) was calculated based on age- and gender-stratified incidences. The SIR in KTRs compared with the general population was 7.9 (95% confidence interval (CI): 6.2–10.0) when averaged for the whole duration of post-transplant follow-up (Table 1).

To determine whether this increased risk was due to the transplantation itself, we calculated SIR for the first post-transplant year, and SIR for later time periods. When only the events and person–time of the first post-transplant year were considered, the SIR for TE in KTRs was 26.1 (95% CI: 17.6–37.5) compared with the general population. After the first post-transplant year, the SIR for TE in KTRs was 5.2 (95% CI: 3.8–7.1) compared with the general population, whereas this ratio was 4.3 (95% CI: 2.6–6.7) after 5 years and 3.9 (95% CI: 1.6–8.1) after 10 years (Figure 2). Our results suggest that the elevated TE risk observed in KTRs is mediated by the initial surgery. However, other factors likely contribute to the increased TE risk observed in our patient population, as the risk remains persistently elevated even after 5–10 years of follow-up.

Compared with the general population, KT conferred a similar increase in risk in both men and women. However, there was a disproportionate increase in TE risk associated with KT in younger compared with older patients (Table 1).

### The risk of TE is partly but not fully explained by an increased probability of hospitalization in KTRs compared with the general population

We questioned whether the augmented TE risk in transplant patients was due to their frequent hospitalizations. When the cases and corresponding person–time that occurred during a hospitalization were excluded ($n = 20$), the SIR decreased to 5.6 (95% CI: 4.2–7.4). Hence, the risk of TE after KT is partly, but not fully, explained by the increased likelihood of KTRs to be hospitalized compared with the general

**Table 1 | Thromboembolic events in kidney transplantation recipients and in the general population**

| | Kidney transplant recipients | | | Reference general population | | | | |
|---|---|---|---|---|---|---|---|---|
| | Events | P–y | Rate per 1000 p–y | Events | P–y | Rate per 1000 p–y | SIR | 95% CI |
| Overall | 67[a] | 6760.02 | 9.91 | 52,699 | 49,794,387 | 1.06 | 7.92 | 6.19–9.99 |
| Women | 26 | 2359.44 | 11.44 | 27,445 | 25,092,214 | 1.09 | 8.89 | 5.93–12.83 |
| Men | 41 | 4400.58 | 9.32 | 25,254 | 24,702,173 | 1.02 | 7.41 | 5.39–9.95 |
| Within first year post transplantation | 27 | 903.52 | 29.88 | 52,699 | 49,794,387 | 1.06 | 26.14 | 17.58–37.50 |
| After first year post transplantation | 39[b] | 5541.14 | 7.04 | 52,699 | 49,794,387 | 1.06 | 5.23 | 3.77–7.08 |
| Age 20–39 years | 16 | 1289.11 | 12.41 | 9268 | 19,751,872 | 0.47 | 27.30 | 16.16–43.39 |
| 40–49 | 13 | 1739.08 | 7.48 | 10274 | 12,421,796 | 0.83 | 9.15 | 5.09–15.25 |
| 50–59 | 24 | 1992.72 | 12.00 | 15047 | 10,585,383 | 1.42 | 8.46 | 5.55–12.40 |
| 60–69 | 14 | 1394.95 | 10.04 | 18110 | 7,035,336 | 2.57 | 3.87 | 2.20–6.34 |

Abbreviations: CI, confidence interval; p-y, person–years; SIR, standardized incidence ratio.
[a]One case that occurred at the age of >70 was excluded because of the low number of patients in that age group.
[b]One case was classified in the >70 age group after 1 year of follow-up because of aging one year. This case was excluded.